FORM PTO-1083

Docket No.: 300.1003US
Date: May 23, 2006

Mail Stop: Appeal Brief
COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

In re application of: Chih-Ming CHEN, et al.
Serial No.: 09/435,576
Filed: November 8, 1999
For: **HMG-COA REDUCTASE INHIBITOR EXTENDED RELEASE FORMULATION**

S i r:

Transmitted herewith is an **APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. §1.192** in the above-identified application.

[ ] Small entity status under 37 C.F.R. 1.9 and 1.27 has been previously established.
[ ] Applicants assert small entity status under 37 C.F.R. 1.9 and 1.27.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

[X] Also transmitted herewith are:
[X] Petition for four (4) month extension under 37 C.F.R. 1.136
[X] Other: References listed on Evidence Appendix

[X] Check(s) in the amount of **$2,090.00** is/are attached to cover:
[] Filing fee for additional claims under 37 C.F.R. 1.16
[X] Petition for four (4) month extension under 37 C.F.R. 1.136
[X] Other: Appeal Brief Fee

[X] The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552.

[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Robert Paradiso by Elizabeth

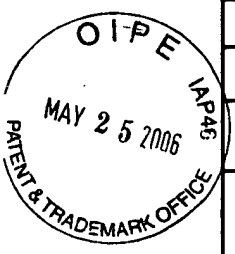
Robert J. Paradiso, Reg. No. 41,240
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

Reg. No 52,124

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with sufficient postage to the United States Postal Service as "first class mail" in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" on May 23, 2006.
DAVIDSON, DAVIDSON & KAPPEL, LLC

BY: _____
Marina Krioutchkova

PTO/SB/22 (10-04)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE



PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2005 (fees effective on or after October 1, 2004)	Docket Number (Optional) 300.1003US
Application Number 09/435,576	Filed November 8, 1999
For HMG-COA REDUCTASE INHIBITOR EXTENDED RELEASE FORMULATION	
Art Unit 1616	Examiner Sharmila S. Gollamudi

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$120	$60	$____
☐ Two months (37 CFR 1.17(a)(2))	$450	$225	$____
☐ Three months (37 CFR 1.17(a)(3))	$1020	$510	$____
☒ Four months (37 CFR 1.17(a)(4))	$1590	$795	$1590
☐ Five months (37 CFR 1.17(a)(5))	$2160	$1080	$____

☐ Applicant claims small entity status. See 37 CFR 1.27.

☒ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-0552 . I have enclosed a duplicate copy of this sheet.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71

Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 41,240

☐ attorney or agent under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34. ____ .

Robert Paradiso by Elizabeth Stewart Reg. No. 52,121 — May 23, 2006

Signature — Date

Robert J. Paradiso — (212) 736-1940

Typed or printed name — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/435,576
Applicant	:	Chih-Ming CHEN, et al.
Filed	:	November 8, 1999
TC/A.U.	:	1616
Examiner	:	Sharmila S. Gollamudi
Docket No.	:	300.1003
Customer No.	:	23280
For	:	**HMG-COA REDUCTASE INHIBITOR EXTENDED RELEASE FORMULATION**

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

May 23, 2006

APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. §1.192

Sir:

Appellants submit this brief for the consideration of the Board of Patent Appeals and Interferences in support of their appeal of the Final Office Action dated July 21, 2005 and the Advisory Actions dated December 22, 2005 and April 26, 2006 in the above-identified application. A Notice of Appeal and a Response under 37 C.F.R. §1.116 were filed on November 21, 2005, and received by the United States Patent and Trademark Office on November 23, 2005. A supplemental response was filed on April 7, 2006 and received by the United States Patent and Trademark Office on April 10, 2006. A second supplemental response has been filed concurrently with the filing of this brief.

Also enclosed herewith is a Petition for a Four Month Extension of Time, extending the time to submit this brief from January 23, 2006 to May 23, 2006, and a check in the amount of $2,090.00, $500.00 of which covers the statutory fee for the submission of this brief and $1,590.00 of which cover the statutory fee for the Petition for a Four Month Extension of Time.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is Andrx Labs LLC, a U.S. company having a place of business at 4955 Orange Drive, Davie, FL 33314, USA, assignee of the entire right, title, and interest in the above-identified patent application; and the licensee, Firt Horizon Pharmaceuticals Corporation, a U.S. company having a place of business at 6195 Shiloh Road, Alpharetta, GA 30005.

The invention was assigned by the inventors Chih-Ming Chen, Joseph Chou, and David Wong to Andrx Corporation. The assignment from the inventors to Andrx Corporation was recorded on November, 8, 1999 at reel 010385, frame 0949. The invention was then assigned from Andrx Corporation to Andrx Labs, LLC. The assignment from Andrx Corporation to Andrx Labs LLC was recorded on February 25, 2003 at reel 013788, frame 0187.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives and assignee are not aware of any appeal or interference that directly affects, will be directly affected by, or will have a bearing on the decision in this appeal.

III. STATUS OF CLAIMS

Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 are pending in this application. No claims have been allowed, all claims being subject to rejections in a Final Office Action dated July 21, 2005, and Advisory Actions dated December 22, 2005 and April 26, 2006, and it is from this Final Office Action (and subsequent Advisory Actions) that this Appeal is taken. Claims 1-13, 18-19, 21-22, 25-29, 31-54 and 76-81 remain in the application and are appealed. A copy of these appealed claims is attached hereto as an Appendix.

IV. STATUS OF AMENDMENTS

In the Response under 37 C.F.R. §1.116 filed November 21, 2005, and the Supplemental Responses filed April 7, 2006 and May 23, 2006, the claims were not amended. In the Advisory Action dated December 22, 2005, the Examiner indicated that the claims remain rejected as set forth in the Final Office Action of July 21, 2005. In the Advisory Action dated April 26, 2006, the Examiner indicated that the rejection under 35 U.S.C. § 112, first paragraph was withdrawn in view of Applicants' arguments.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A. Claim 1

Independent claim 1 recites a controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a drug comprising an alkyl ester of hydroxy substituted naphthalenes. See specification *e.g.* at page 3, lines 7-13.

Claim 1 further recites that the dosage form comprises a controlled release carrier in an amount effective to provide a controlled release of the drug. See specification *e.g.* at page 4, lines 13-14.

Claim 1 further recites the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration to human patients. See specification *e.g.* at page 4, lines 15-16 and page 19, lines 39-42.

Claim 1 further recites the dosage form providing a reduction in serum cholesterol levels when administered to human patients on a once-a-day basis. See specification *e.g.* at page 4, lines 17-18 and Table 12 at page 52.

B. Claim 48

Independent claim 48 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form. See specification *e.g.* at page 3, lines 22-28.

The method of claim 48 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32

hours after oral administration of the dosage form to human patients. See specification *e.g.* at page 4, lines 15-16 and page 19, lines 39-42.

C. Claim 58

Independent claim 58 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients at dinner time. See specification *e.g.* at page 8, lines 16-18.

Claim 58 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) at 10.4 to about 20.6 hours after oral administration of a single dose to a population of human patients. See specification *e.g.* at page 8, lines 19-20.

D. Claim 62

Independent claim 62 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients at bedtime. See specification *e.g.* at page 9, lines 1-3.

The method of claim 62 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours after oral administration. See specification *e.g.* at page 9, lines 4-5.

E. Claim 70

Independent claim 70 recites a method for improving the dose-response relationship achieved via the administration of a statin drug orally administered in immediate release form. See specification *e.g.* at page 9, lines 22-23.

The method of claim 70 further recites by orally administering the statin in a controlled release dosage form which provides a mean time to maximum plasma concentration (T_{max}) of the statin drug which occurs at 10 to about 32 hours after oral administration to human patients. See specification *e.g.* at page 9, lines 24-26.

F. Claim 71

Independent claim 71 recites a method for providing increased systemic bioavailability of lovastatin, while at the same time not increasing the bioavailability of lovastatin acid, compared to an immediate release reference standard form of lovastatin. See specification *e.g.* at page 10, lines 22-25.

The method of claim 71 recites the step of preparing a controlled release oral solid dosage form of lovastatin which comprises a therapeutically effective amount of lovastatin and a sufficient amount of a controlled release carrier. See specification *e.g.* at page 10, lines 25-27.

The method of claim 71 further recites that the dosage form provides a dissolution of:

from about 0% to about 25% lovastatin released after 2 hours; see specification *e.g.* at page 10, lines 27-28;

from about 40% to about 85% lovastatin released after 6 hours; see specification *e.g.* at page 10, lines 28-29; and

not less than about 75% lovastatin released after 16 hours; see specification at page 10, line 29.

The dissolution rate recited in claim 71 is measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C and 50rpm. See specification *e.g.* at page 11, lines 1-2.

The method of claim 71 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin from 10 to about 32 hours after

oral administration to human patients, and administering the dosage form to human patients on a once-a-day basis. See specification *e.g.* at page 11, lines 2-5.

G. Claim 76

Independent claim 76 recites a controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The controlled release carrier of claim 76 is present in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered. See specification *e.g.* at page 4, lines 13-14.

Claim 76 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime. See specification *e.g.* at page 45, Table 6.

H. Claim 77

Independent claim 77 recites a controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The controlled release carrier of claim 77 is present in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered. See specification *e.g.* at page 4, lines 13-14.

Claim 77 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.6 to about 23.2 (16.9 ±

6.3) hours after oral administration to human patients at bedtime. See specification *e.g.* at page 45, Table 6.

I. Claim 78

Independent claim 78 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The method of claim 78 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime. See specification *e.g.* at page 45, Table 6.

J. Claim 79

Independent claim 79 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The method of claim 79 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.6 to about 23.2 (16.9 ± 6.3) hours after oral administration to human patients at bedtime. See specification *e.g.* at page 45, Table 6.

K. Claim 80

Independent claim 80 recites a controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The controlled release carrier of claim 80 is present in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered. See specification *e.g.* at page 4, lines 13-14.

Claim 80 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal. See specification *e.g.* at page 45, Table 6.

L. Claim 81

Independent claim 81 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The method of claim 81 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal. See specification *e.g.* at page 45, Table 6.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are presented for appeal:

(1) Claims 1-13, 18, 19, 21, 22, 25-54, 57-71, and 76-81 have been rejected under 35 U.S.C. § 102(b) on the grounds of being anticipated by U.S. Patent No. 5,376,383 to Alberts et al.

(2) Claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71, and 76-81 have been rejected under 35 U.S.C. § 103(a) on the grounds of being obvious over U.S. Patent No. 5,837,379 to Chen et al.

(3) Claims 1-13, 18, 19, 21, 22, 25-47, 76-77, and 80 have been rejected on the grounds of being unpatentable under the judicially created doctrine of obvious-type double patenting over claims 1-12 of U.S. Patent No. 6,485,748 to Chen et al.

(4) Claims 1-13, 18-19, 21-22, 25-47, 76-77, and 80 have been rejected on the grounds of being unpatentable under the judicially created doctrine of obvious-type double patenting over the claims of co-pending Application No. 09/435,576. Appellants note that Application No. 09/435,576 corresponds to the instant application, and believe that this is a typographical error. Accordingly, Appellants will address this rejection with respect to co-pending Application No. 10/603,254.

VII. ARGUMENT

A. 35 U.S.C. §102 Rejection of Claims 1-13, 18-19, 21-22, 25-54, 57-71, and 76-81 Based Upon U.S. Patent No. 5,376,383 to Alberts et al.

1. The Examiner's rejection

The first issue presented is whether claims 1-13, 18, 19, 21, 22, 25-54, 57-51, and 76-81 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,376,383 to Alberts et al. (hereinafter "the Alberts reference"). In the Final Office Action, the Examiner stated the following:

> Alberts discloses a method of lowering plasma cholesterol levels by administering to a subject a time-controlled drug-delivery device containing a water-soluble HMG-CoA reductase inhibitor (lovastatin, pravastatin, etc.). Alberts discloses that using a sustained or controlled release provides for a single dose to yield an equivalent or improved effect as that of a rapid release formulation (col. 1, lines 39-50 and abstract). . . . The examples provide a controlled device comprising a core and a coat, which is substantially similar to instant disclosure Table 1's general formula.
>
> Note that although the prior art does explicitly state the instant functional limitations, it is the examiner's position that the instant functional limitation is inherent since Albert's example 10 provides a release rate over an 18 hour period. Thus, the Tmax would inherently fall within [the] instant range. The recitation of a newly discovered function inherently possessed by the prior art, doe not make distinguish it from the prior art. Further it is applicant's burden to prove otherwise.

Final Office Action of July 21, 2005 at pages 3-4 (*citations omitted*).

In the December 22, 2005 Advisory Action, the Examiner responded to Appellants' arguments in the November 21, 2005 Response to Final Office Action, as follows:

> With regard to the 102 rejection over Alberts, the examiner points out that, the examiner has made a reasonable rationale for inherency and it is the applicants burden to prove it is not inherent with evidence. Note MPEP 716.01 II wherein it clearly states that the attorney arguments cannot [take] the place of evidence.

Advisory Action of December 22, 2005 at page 2.

In the April 26, 2006 Advisory Action, the Examiner responded to Appellants' arguments presented in the April 7, 2006 Supplemental Response as follows:

> As indicated in the Final Office Action, Table 1 provides the structure, which provides the instant functional limitations. The device provided in Table 1 only requires a core and an outer coating. The seal coat, an inner coat, and overcoat are not required since the claimed range encompasses zero. Zero clearly implies that the coating is not required. Therefore, examiner points out that the instant structure as defined in Table 1 and that of the prior art are substantially the same used for the same purpose. With regard to the water-soluble polymer, Alberts examples utilize a water soluble polymer in the core. Therefore, the examiner has made a reasonable rationale for inherency. With regard to McClelland's structure is not similar to Albert's structure as argued by applicant.

Advisory Action of April 26, 2006 at page 2.

2. U.S. Patent No. 5,376,383 to Alberts et al. does not anticipate the claims

a. Claims 1-13, 18-19, 21-22, 25-54, 57-71, and 76-81

Appellants respectfully submit that the Alberts reference does not inherently teach the claimed T_{max} parameters as recited in the present claims.

Specifically, the Alberts reference does not inherently teach a controlled release dosage form of the present invention or a method of treatment with a controlled release dosage form of the present invention, which provides the following:

a. a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration as recited in claims 1, 48, 70, and 71;

b. a mean time to maximum plasma concentration (T_{max}) which occurs at about 11 to about 32 hours after oral administration as recited in claim 51;

c. a mean time to maximum plasma concentration (T_{max}) at 10.4 to about 20.6 hours after oral administration as recited in claim 58;

d. a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours as recited in claim 62;

e. a mean time to maximum plasma concentration (T_{max}) of lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime as recited in claims 76 and 78;

f. a mean time to maximum plasma concentration (Tmax) of lovastatin which occurs at 10.6 to 23.2 (16.9 ± 4.5) hours after oral administration to human patients at bedtime as recited in claims 77 and 79; or

g. a mean time to maximum plasma concentration (Tmax) of lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal as recited in claims 80 and 81.

In support of this position, submitted herewith is Gregory A. McClelland, et al., Enhancement of 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Efficacy Through Administration of a Controlled-Porosity Osmotic Pump Dosage Form, Pharmaceutical Research, Vol. 8., No. 7. 1991, which was submitted in the Appellants response dated April 7, 2006. Contrary to the Examiner's position that the McClelland structure is not similar to Albert's structure, Appellants respectfully submit that the McClelland structure and the Alberts structure are virtually identical. For

example, page 874 of McClelland, et al. describes a formulation which contains the same ingredients as the formulation described in Example 3 of Alberts as indicated in Table A below:

TABLE A

Table I of McClelland (Core Ingredients)[1]	Example 3 of Alberts (Core Ingredients)
Tromethammonium II[2]	7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)dimethyl-8(S)-(2,2-dimethylbutyrylox y)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)methylammonium salt
Tromethamine Free Base	Tromethamine Free Base
Mannitol	Mannitol
Dowex 50x8	Dowex 50x8
Povidone 29-32K[3]	Polyvinylpyrrolidone
BHA[4]	Butylated hydroxyanisole
Mg. Stearate[5]	Magnesium stearate
(Coating Ingredients)	(Coating Ingredients)
CA-398-30[6]	Cellulose acetate (39% acetyl content)
CA-320S[7]	Cellulose acetate (32% acetyl content)
Sorbitol	Sorbitol
PEG 400[8]	polyethylene glycol 400

[1] The order of the ingredients in Table A is different than listed in McClelland et al. to facilitate comparison with Example 3 of Alberts.
[2] The tris(hydroxymethyl)methylammonium salt of Compound II in McClelland et al., i.e., 7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)dimethyl-8(S)-(2,2-dimethylbutyrylox y)-naphthalenyl-1(S)]-3(R),5(R)-dihydroxyheptanoate tris(hydroxymethyl)methylammonium salt, the same agent as in Example 3 of Alberts.
[3] Polyvinylpyrrolidone
[4] butylated hydroxyanisole
[5] magnesium stearate
[6] cellulose acetate (39% acetyl content)
[7] cellulose acetate (32% acetyl content)
[8] polyethylene glycol

Further, it is noted that the ratio of the core ingredients in Example 3 of Alberts[9] (in the order of ingredients in Table A above, not including magnesium stearate) is:

1 : 4.13 : 3.94 : 1.97 : 0.98 : 0.0024

The amount of core ingredients in Table I of McClelland et al. (in the order of ingredients in Table A above, not including magnesium stearate) is 25.4 mg, 105 mg, 100 mg, 45 mg, 25 mg, 0.06 mg, and 1.6 mg, respectively. This is a ratio of:

1 : 4.13 : 3.94 : 1.77 : 0.98 : 0.0024

which is virtually identical to the ratio in Example 3 of Alberts (with the exception of the 1 : 1.97 ratio in Alberts as compared to the 1 : 1.77 ratio in McClelland). Also, Alberts describes magnesium stearate used in 0.5% w/w which is the same amount used in Table 1 of McClelland et al.[10]

With respect to the coating ingredients, it is noted that the ratio of the core ingredients in Table I of McClelland[11] (in the order of ingredients in Table A above) is:

1 : 0.33 : 0.96 : 0.27

The amount of coating ingredients in Example 3 of Alberts (in the order of ingredients in Table A above) is 54 mg, 18 mg, 52 mg and 14.4 mg, respectively. This is a ratio of:

1 : 0.33 : 0.96 : 0.27

which is identical to the ratio in Table I of McClelland.

---

[9] See column 7, line 39 of Alberts.
[10] The total weight of the core in Table I of McClelland (not including the magnesium stearate) is about 300 mg. The magnesium stearate is in an amount of 1.5 mg which equals about 0.5%.
[11] See last column of Table I, page 874 of McClelland et al.

Also, a comparison of the processing procedures in Alberts and McCelland et al. shows that virtually identical steps are included. For example, both procedures *(i)* form a core tablet with a 3/8-in. standard concave die (column 7, line 42 of Alberts; page 874, column 1, line 26 of McClelland et al.), and *(ii)* apply a 350 micrometer coat to the core tablet utilizing a water: methanol: methylene chloride solvent blend in a 1:10:15 ratio (column 7, lines 50-52 of Alberts; page 874, footnote (a) of Table I of McClelland et al.).

As established above, the formulation of Example 3 of Alberts is virtually identical to the formulation of McClelland et al.

McClelland et al. demonstrate *in vivo* data with respect to this formulation in Figure 2 on page 875, which depicts the peak of the plasma/concentration time curve at a time less than 5 hours. One skilled in the art would immediately recognize that this is not indicative of the T_{max} recited in the presently claimed invention (e.g., 10 to about 32 hours), to the extent that dog data is instructive with respect to humans.

Therefore, assuming arguendo that the Examiner has provided a reasonable rational to establish inherency, Appellants respectfully submit that they have met their burden to prove that the pharmacokinetic parameters are not inherent with evidence, as requested by the Examiner. The evidence provided by Appellants shows that Example 3 of Alberts is virtually identical to the formulation of McClelland et al. and that the in-vivo data in McClelland at al. is not indicative of the T_{max} of the present invention (e.g., 10 to about 32 hrs). Therefore, by syllogism, Example 3 of Alberts would not inherently be indicative of the recited T_{max} (e.g., 10 to about 32 hrs), as it is virtually identical to the McClelland formulation.

Appellants submit that they have established that the claimed pharmacokinetic parameters are not inherent in the Alberts reference. In any event, Appellants respectfully submit that the Examiner did not establish a reasonable rationale that the

claimed pharmacokinetic parameters were inherent in the Alberts reference. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). See also, *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Appellants respectfully submit that the Examiner did not meet her burden of proof to make an inherency rejection, as there is no indication in the Alberts reference that the claimed T_{max} of the present invention must be "necessarily present" in the formulations described in the reference. It is further submitted that if one of ordinary skill in the art were able to manipulate the formulations of Alberts to achieve a formulation which met the present claimed limitations, one would have to optimize conditions, ingredients and parameters. For example, critical parameters such as compression force, particle size of initial ingredients, and temperature/humidity conditions are not specified in the Alberts reference.

For example, the Examiner appears to conclude that formulating an alkyl ester of a hydroxy substituted naphthalene into a controlled release dosage form will necessarily provide the claimed T_{max} ranges (e.g., 10 to about 32 hours). To support her position that the Alberts reference inherently describes the presently claimed T_{max}, the Examiner cited Example 10 of the Alberts reference in the July 21, 2005 Final Office Action. However, Example 10 merely states that the formulation gave an 85% release over 18 hours, and fails to provide any indication or suggestion for correlating a mean time to maximum plasma concentration (T_{max}). "[A]nticipation by inherent disclosure is appropriate only

when the reference discloses prior art that must necessarily include the unstated limitation." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006). Appellants submit that an 85% release over 18 hours does not indicate that the formulation therein "must necessarily including the unstated limitation", *i.e.* the claimed mean time to maximum plasma concentration (T_{max}). Appellants respectfully disagree. For example, a formulation which provides an initial burst of active agent within the first few hours, could have an early T_{max} (e.g., 1 or 2 hours) while still releasing 85% active agent at 18 hours.

In further support this position, Appellants enclose a copy of pages 2730-2735 of The Physician's Desk Reference, 2006 Edition, which describes the product information for Lescol XL®, which was submitted in Appellants' May 23, 2006 supplemental response. Lescol XL® is a once-a-day controlled release dosage form of fluvastatin, an alkyl ester of a hydroxy substituted naphthalene. As indicated at page 2731, first column, Lescol XL® provides peak concentration of fluvastatin within 2.5 to 3 hours post dose (i.e., a T_{max} of 2.5 to 3 hours). This is in contrast to the T_{max} ranges (e.g., 10 to about 32 hours) provided by the present invention. In view of this information, Appellants respectfully submit that including a hydroxy substituted naphthalene into a controlled release dosage form will not inherently provide the claimed T_{max} ranges (e.g., 10 to about 32 hours).

Further, the Examiner's "reasonable rationale" for establishing inherency is based on the misconception that the Alberts examples and the general formula of Table I of the present application are substantially the same. However, the formulations described by Alberts are remarkably different from those taught by the present application and therefore the conclusion that the Alberts formulations inherently disclose the pharmacokinetic parameters and dissolution profiles of the claimed controlled release dosage forms is incorrect.

Table I of the present application shows that a tablet that can be modified to exhibit the claimed pharmacokinetic parameters can contain a) an inner core containing an alkyl ester of a substituted naphthalene, a water swellable polymer, and an osmotic agent and b) an outer coating containing an enteric polymer and a water-insoluble polymer. In contrast, Alberts describes tablets with cores that **do not** contain water swellable polymers (examples 3-7) and tablets that contain drug mixed with a water swellable polymer, but **do not** have an outer coating containing an enteric polymer and a water-insoluble polymer (examples 8-16).

The Examiner alleges that the coating is not required because Table I includes ranges which encompass zero. However, Appellants submit that the claims are not meant to encompass any formulation that may fall within the general ranges of Table I of the present application. Rather, the claims are meant to encompass only those formulations which exhibit the claimed T_{max} parameters. The exemplified formulations which exhibit the pharmacokinetic data of the instant claims contain a core, a seal coat, an inner coating containing an enteric polymer, an outer coating containing an enteric polymer and a water insoluble polymer, and an optional overcoat (see examples 5-9 on pages 35-38; pages 40-44; and tables 6-8). It is noted that the present claims are not limited to these exemplified formulations and that other formulations which exhibit the claimed pharmacokinetic parameters are encompassed by the claimed invention. For example, pages 19 to 24 of the present specification disclose many different types of formulations which can be modified to provide the claimed pharmacokinetic parameters.

In accordance with the above, Appellants respectfully submit that the Alberts reference does not teach or suggest the presently claimed compositions and methods which recite the claims T_{max} limitations.

In addition, Appellants respectfully submit that the Alberts reference does not teach or suggest the claimed method for improving the dose-response relationship achieved via the administration of a statin drug orally administered in immediate release form as recited in claim 70.

Appellants further submit that the Albert reference does not teach or suggest the claimed method for providing increased systemic bioavailability of lovastatin, while at the same time not increasing the bioavailability of lovastatin acid, compared to an immediate release reference standard form of lovastatin as recited in claim 71. The Alberts reference also does not teach or suggest the claimed dissolution parameters as recited in claim 71.

Accordingly, Appellants respectfully request that the rejection over the Alberts reference be removed.

B. 35 U.S.C. §103 Rejection of Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 Based Upon U.S. Patent No. 5,837,379 to Chen et al.

1. The Examiner's rejection

The second issue presented is whether claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 are unpatentable under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,837,379 to Chen et al.

In the final Office Action, the Examiner stated the following:

> Chen et al disclose a once daily pharmaceutical tablet having a 1) compressed core contains a medicament, a water-soluble osmotic compound, and one or more osmotic polymers, and 2) a membrane coating containing a water insoluble pharmaceutically acceptable polymer and an enteric polymer. See abstract. Although nifedipine is exemplified, Chen teaches various water-insoluble medicaments that may be utilized, including instant lovastatin. See column 2, line 64.
>
> . . . .
>
> It is deemed obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Chen et al and include the instant lovastatin in the controlled release dosage form. One

> would have been motivated to do so since Chen teaches a variety of medicaments that would benefit from the use of the instant controlled release formulation and teaches the instant active as one of the suitable medicaments. Therefore, one could reasonably expect similar results by including lovastatin in Chen's controlled release device.
>
> Furthermore, it is the examiner position that the instant controlled release device would meet the instant functional limitations since Chen's controlled release device is similar in structure and formulation to applicant's dosage form described in the specification; in particular Table 1. Therefore, it is the examiner's position that both would function similarly if not the same since the structures of the instant invention and that of the prior art are the same.

Final Office Action of July 21, 2005 at pages 7-8.

In the December 22, 2005 Advisory Action, the Examiner responded to Appellants' arguments in the response to Final Office Action as follows:

> With regard to the obviousness rejection over Chen, the examiner has not argued that nifedipine and lovastatin have similar structures, rather the examiner has argued that the controlled release dosage form taught by Chen is structurally similar to applicant's. Thus it is the examiner's position that the controlled release dosage form would provide the instantly claimed Tmax. The examiner notes that lovastatin is not exemplified and is taught as a suitable drug among other drugs, thus the examiner has made the rejection under obviousness wherein the criteria for obviousness is that the prior art provides some suggestion or motivation to utilize the instantly claimed drug. In instant case, Chen teaches lovastatin is a suitable drug to utilize in the dosage form.

Advisory Action of Dec. 22, 2005 at page 2.

In the April 26, 2006 Advisory Action, the Examiner responded to Appellants' arguments in the April 7, 2006 Supplemental Response as follows:

> Although the pharmacokinetics of nifedipine are exemplified, a skilled artisan [] would have been motivated to substitute nifedipine with the instant lovastatin and expect similar pharmacokinetic values since Chen clearly suggests the use of other drugs in place of nifedipine.

April 26, 2006 Advisory Action at pages 2-3.

2. U.S. Patent No. 5,837,379 to Chen et al. does not render the claims obvious

a. Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81

Appellants respectfully submit that Chen et al. fail to teach or suggest the present formulation comprising an alkyl ester of hydroxy substituted naphthalenes with the claimed pharmacokinetic parameters.

In rejecting the claims over Chen et al., the Examiner appears to conclude that formulating an alkyl ester of a hydroxyl substituted naphthalene into a controlled release dosage form will necessarily provide the claimed T_{max} ranges (e.g., 10 to about 32 hours) and that the claimed T_{max} ranges are generally known to be desirable for alkyl esters of a hydroxy substituted naphthalene. Appellants respectfully disagree. In support of this position, Appellants enclose a copy of pages 2730-2735 of The Physician's Desk Reference, 2006 Edition, which describes the product information for Lescol XL®, which was submitted in Appellants' May 23, 2006 supplemental response. Lescol XL® is a once-a-day controlled release dosage form of fluvastatin, an alkyl ester of a hydroxy substituted naphthalene. As indicated at page 2731, first column, Lescol XL® provides peak concentration of fluvastatin within 2.5 to 3 hours post dose (i.e., a T_{max} of 2.5 to 3 hours). This is in contrast to the T_{max} ranges (e.g., 10 to about 32 hours) provided by the present invention. In view of this information, Appellants respectfully submit that including a hydroxyl substituted naphthalene into a controlled release dosage form will not inherently provide the claimed T_{max} ranges (e.g., 10 to about 32 hours) and that the claimed T_{max} ranges are not generally known as desirable for alkyl esters of a hydroxy substituted naphthalene.

Appellants respectfully submit that Chen et al. fail in the very least to teach, hint or suggest the T_{max} range recited in the present claims. The only data provided in this patent directed to in-vivo results is data directed to dosage forms of nifidepine, which is not in any way related to, e.g., HMG-CoA Reductase Inhibitors. None of the exemplified

formulations include a drug that is a HMG-CoA Reductase Inhibitor, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone a HMG-CoA Reductase Inhibitor. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that the in-vivo plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxy substituted napthalenes.

Appellants respectfully submit that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner used impermissible hindsight reasoning in making this rejection.

The physical characteristics (e.g., solubility, melting point) for any given drug are typically different. These characteristics must be considered in formulating the drug. Chen et al. does not exemplify any formulations containing an alkyl ester of hydroxy substituted naphthalene, nor does it provide any specific guidance with respect to formulating such an agent. For example, there is no teaching of compression forces or temperature and humidity processing parameters for preparing a formulation containing an alkyl ester of hydroxy substituted naphthalene. Therefore, assuming one skilled in the art could formulate an alkyl ester of hydroxy substituted naphthalene in accordance with the teachings of Chen et al. to achieve the claimed T_{max} parameters, such formulation would be a result of optimization of conditions. Therefore the Examiner is incorrect to state that "... both would function similarly if not the same since the structures of the instant invention and that of the prior art are the same." See *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Further, Appellants note that the foundational facts for a prima facie case of obviousness are: (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; and (3) the level of ordinary skill in the art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Moreover, objective indicia such as commercial success and long felt need are relevant to the determination of obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 U.S.P.Q. (BNA) 231, 236 (Fed. Cir. 1983).

Chen et al. is directed to controlled release dosage forms and only incidentally mentions lovastatin, fluvastatin, simvastatin, and pravastatin in an exhaustive list (see column 2, line 51 to column 3, line 11 of Chen et al.) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (*e.g.*, salts, esters, etc.) and there is no motivation in Chen to produce dosage forms of these compounds having the claimed pharmacokinetic parameters. In contrast, the present application clearly demonstrates the benefits and need for these dosage forms in Table 12, which shows the advantage of a formulation of the present invention (Lovastatin XL) over immediate release Mevacor®, with respect to changes in LDL- cholesterol, HDL-cholesterol, Total Cholesterol, and Triglycerides.

Appellants respectfully submit that one skilled in the art would not be motivated to select the particular claimed agent (i.e., an alkyl ester of hydroxy substituted naphthalenes) from the large genus disclosed at column 2, line 51 to column 3, line 11 of Chen et al. In support of this position, it is respectfully submitted that with respect to Chen et al., (i) the size of the genus is not sufficiently small as to render each member of the genus inherently disclosed, (ii) the reference does not expressly teach a particular reason to select the claimed agent; and (iii) there is no teaching of structural similarity in the reference. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(A-C). A discussion of these points follows:

(i) The size of the genus is not sufficiently small as to render each member of the genus inherently disclosed

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Some motivation to select the claimed species or subgenus must be taught by the prior art. See *e.g.*, *In re Deuel*, 51 F.3d 1552, 1558-59, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

It is respectfully submitted that the size of the possible active agents which can be used in accordance with Chen et al. is sufficiently large as not to inherently disclose each and every individual species (in this case, lovastatin, fluvastatin, simvastatin, and pravastatin) which falls within their broad genus.

(ii) The reference does not expressly teach a particular reason to select the claimed agent

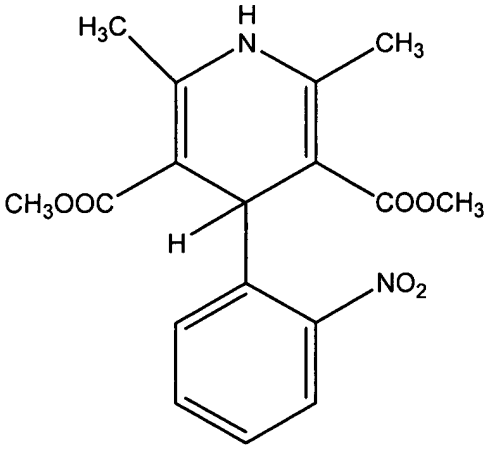
If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(B). It is respectfully submitted that the only recitation of lovastatin, fluvastatin, simvastatin, and pravastatin in Chen et al. is embedded within a large genus. Accordingly, the Chen et al. reference does not expressly teach a particular reason to select an alkyl ester of hydroxy substituted naphthalenes, such as lovastatin, from the plethora of other possible species in the genus of the reference.

(iii) There is no teaching of structural similarity in the reference

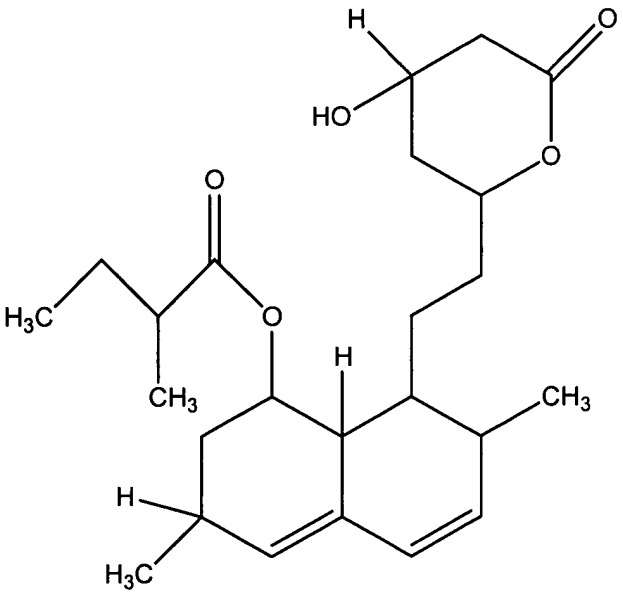
If a preferred species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species from the genus. See, *e.g.*, *In re Dillon*, 919 F.2d 688, 693, 696, 16 USPQ2d 1897, 1901, 1904 (Fed. Cir.

1990). It is noted that the preferred active agents exemplified in Chen et al. is nifedipine in Examples 1 and 2.

It is respectively submitted that nifedipine is not similar in structure to lovastatin, fluvastatin, simvastatin, and pravastatin (the alkyl esters of hydroxy substituted naphthalenes described in Chen et al.) and does not provide similar pharmacological activity. Nifedipine is a calcium channel blocker which is used primarily for the treatment of hypertension, while lovastatin, fluvastatin, simvastatin, and pravastatin are HMG COA reductase inhibitors for the treatment of hypercholesterolemia. Structurally, nifedipine is a dihydropyridine compound and lovastatin, fluvastatin, simvastatin, and pravastatin are lactone based structures. In order to exemplify, the structures of these lovastatin and nifedipine are set forth below in order to show the dissimilar structures of these agents:



Nifedipine



Lovastatin

Accordingly, as Chen et al. does not teach any preferred species which have structural similarity to lovastatin, fluvastatin, simvastatin, and pravastatin, there is no

motivation therein to one skilled in the art to select these agents from the large genus disclosed therein.

Although the Examiner stated that she has not argued that nifedipine and lovastatin have similar structures, but that the controlled release dosage form taught by Chen et al is structurally similar to Appellants', the structure of the controlled release dosage form would ultimately be altered with the inclusion of lovastatin. The differences in structure, pharmacological properties, and characteristics, of the species of active agent would be considered by one or ordinary skill in the art in the preparation of a controlled release formulation. Any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. See, *e.g.*, *In re Baird*, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir. 1994). Accordingly, the examples of Chen et al. directed to a compound (i.e. nifedipine) that is not structurally similar to lovastatin, fluvastatin, simvastatin, and pravastatin (as discussed above) is further evidence that one skilled in the art would not be motivated to select these compounds from the genus described therein.

The broad ranges described in the present specification at Table 1 provide guidance to one of ordinary skill in the art to prepare a dosage form of the present invention with routine experimentation. One skilled in the art would appreciate that formulations of alkyl esters of hydroxy substituted naphthalenes could be prepared that do not meet the limitations of claim 1, but would generically fall with the ranges of Table 1 of the present application.

In accordance with the above, Appellants respectfully submit that Chen at al. does not teach or suggest the presently claimed compositions and methods which recite the claimed T_{max} limitations.

In addition, Appellants respectfully submit that Chen et al. does not teach or suggest the claimed method for improving the dose-response relationship achieved via

the administration of a statin drug orally administered in immediate release form as recited in claim 70.

Appellants further submit that Chen et al. does not teach or suggest the claimed method for providing increased systemic bioavailability of lovastatin, while at the same time not increasing the bioavailability of lovastatin acid, compared to an immediate release reference standard form of lovastatin as recited in claim 71. Chen et al. also does not teach or suggest the claimed dissolution parameters as recited in claim 71.

Therefore, as Chen et al. fails to teach or suggest the presently claimed invention, Appellants respectfully submit that the claims are patentable over Chen et al. and respectfully request that this rejection be reversed.

C. Obviousness-Type Double Patent Rejections based upon U.S. Patent No. 6,485,748.

1. The Examiner's rejection

The third issue presented is whether claims 1-13, 18, 19, 21, 22, 25-47, 76-77, and 80 are unpatentable over claims 1-12 of U.S. Patent No. 6,485,748 under the judicially created doctrine of obviousness-type double patenting. In the Final Office Action, the Examiner stated that "[a]lthough US patent '748 recites a generic slightly water-soluble drug, the specification defines lovastatin as a drug that falls within this category.

In the December 22, 2005 Advisory Action, the Examiner stated that ". . . the examiner notes that US patent does not claim the instant Tmax, however, the examiner notes that US patent's claimed dosage form is capable of providing the instantly claimed Tmax."

2. The double patenting rejection over U.S. Patent No. 6,485,748 should be reversed.

a. Claims 1-13, 18, 19, 21, 22, 25-47, 76-77

Appellants note that when considering when the invention defined in the claim of an application is an obvious variation of the invention defined in the claims of a patent, the disclosure of the patent may not be used as prior art. However, the specification can be used as a dictionary to learn the meaning of a term in the patent claim, or be examined with respect to those portions which provide support for the claims (See MPEP 8th Edition, Revision 2, Section 804(2)(B)(1)).

It is respectfully submitted that the claims of the '748 patent fail in the very least to teach, hint or suggest the T_{max} ranges recited in the present claims. In addition, there are no dependent claims directed to alkyl esters of hydroxy substituted naphthalenes or even the general class of HMG CoA reductase inhibitors. In fact, the only dependent claims directed to specific drugs are directed to calcium channel blockers (claims 2 and 3). Furthermore, the specification of the '748 patent, like that of the Chen et al. '379 patent, only incidentally mentions lovastatin, fluvastatin, simvastatin, and pravastatin in an exhaustive list (see column 2, line 58 to column 3, line 16 of the '748 patent) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (*e.g.*, salts, esters, etc.). The only in-vivo data provided in the '748 patent is data directed to dosage forms of nifidepine, which is not in any way related to, *e.g.*, an alkyl ester of hydroxy substituted naphthalenes, as described above. None of the exemplified formulations include a drug that is an alkyl ester of hydroxy substituted naphthalenes, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone an alkyl ester of hydroxy substituted naphthalenes. Moreover, there is no statement in either the specification or the claims of the '748 patent relating to T_{max}, or suggestion that the in-vivo plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxy substituted napthalenes.

Appellants respectfully submit that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner used impermissible hindsight reasoning in making this rejection.

Therefore, it is respectfully submitted that the claims of the '748 patent do not teach or suggest the presently claimed invention Appellants respectfully request that the obviousness rejection over the '748 patent be reversed.

4. **Obviousness Type Double Patenting Rejection Over Co-pending Application No. 09/435,576**

With respect to the double-patenting rejection of the claims over co-pending Application No. 09/435,576, Appellants note that the application number appears to be a typographical error, as Application No. 09/435,576 corresponds to the instant application. Therefore, Appellants address this rejection with respect to co-pending Application No. 10/603,254, and note that a terminal disclaimer over this co-pending application was submitted in the response dated May 23, 2006. Appellants request that the rejection be removed.

Conclusion

Appellants respectfully submit that for the foregoing reasons the final rejections of claims should be reversed, and that the present claims are in condition for allowances

Prompt consideration of the arguments presented herein and reversal of the final rejections is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: Robert Paradiso by Elizabeth Petrosel Reg. No 52,121
Robert J. Paradiso
Reg. No. 41,240

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, NY 10018
Tel: (212) 736-1940

VIII. CLAIMS APPENDIX

Claim 1. (Previously presented) A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a drug comprising an alkyl ester of hydroxy substituted naphthalenes and a controlled release carrier in an amount effective to provide a controlled release of the drug, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration to human patients, the dosage form providing a reduction in serum cholesterol levels when administered to human patients on a once-a-day basis.

Claim 2. (Previously presented) The controlled release oral solid dosage form of claim 1, which includes an amount of a controlled-release carrier for said drug effective to release said drug in about 4 to 30 hours in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37° C and 50rpm.

Claim 3. (Original) The controlled release oral solid dosage form of claim 1, which provides a dissolution of from about 0% to about 25% drug released after 2 hours; from about 40% to about 85% drug released after 6 hours; and not less than about 75% drug released after 16 hours, when measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37° C and 50rpm.

Claim 4. (Original) The controlled release oral solid dosage form of claim 1, which provides a dissolution of from about 0% to about 20% drug released after 2 hours; from about 50% to about 80% drug released after 6 hours; and not less than about 80% drug

released after 16 hours, when measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C and 50rpm.

Claim 5. (Original) The controlled release oral solid dosage form of claim 1, which provides a dissolution of from about 10% to about 15% drug released after 2 hours; from about 65% to about 75% drug released after 6 hours; and not less than about 79% drug released after 16 hours, when measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C and 50rpm.

Claim 6. (Original) The controlled release oral solid dosage form of claim 1, which provides a mean time to maximum plasma concentration about 14 to about 24 hours after oral administration.

Claim 7. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin, said dosage form providing a mean maximum plasma concentration (C_{max}) of lovastatin from about 1 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients.

Claim 8. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin, said dosage form providing a maximum plasma concentration (C_{max}) of the drug of from about 3 ng/ml to about 4 ng/ml (based on a 40 mg dose of lovastatin), after administration to human patients.

Claim 9. (Previously presented) The controlled release dosage form of claim 1, wherein the drug is selected from the group consisting of lovastatin, mevastatin, pravastatin, simvastatin, and mixtures thereof.

Claim 10. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin.

Claim 11. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin in an amount of from about 10 to about 80 mg.

Claim 12. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin, and the dosage form provides a mean $AUC_{0\text{-}48hr}$ of lovastatin from about 15 to about 90 ng·hr/ml.

Claim 13. (Original)The controlled release dosage form of claim 1, wherein the drug is lovastatin, and the dosage form provides a mean $AUC_{0\text{-}48hr}$ of lovastatin from about 34 to about 77 ng·hr/ml.

Claims 14-17. (Cancelled)

Claim 18. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin and the dosage form provides a mean $AUC_{0\text{-}48hr}$ of lovastatin acid from about 9.96 to about 132.54 ng·hr/ml.

Claim 19. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin and the dosage form provides a mean $AUC_{0\text{-}48hr}$ of lovastatin acid from about 47.5 to about 91.2 ng·hr/ml.

Claim 20. (Cancelled)

Claim 21. (Previously presented) The controlled release dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of total HMG-CoA Reductase Inhibitors from about 4.7 ng/ml to about 25.4 ng/ml, based on a 40 mg dose of lovastatin.

Claim 22. (Previously presented) The controlled release dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of total HMG-CoA Reductase Inhibitors from about 10.5 ng/ml to about 17.3 ng/ml, based on a 40 mg dose of lovastatin.

Claims 23-24. (Cancelled)

Claim 25. (Previously presented) The controlled release dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of active HMG-CoA Reductase Inhibitors from about 2.1 ng/ml to about 22.5 ng/ml, based on a 40 mg dose of lovastatin.

Claim 26. (Previously presented) The controlled release dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of active HMG-CoA Reductase Inhibitors from about 6.4 ng/ml to about 13.4 ng/ml.

Claim 27. (Original) The controlled release oral solid dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) which occurs at about 11 to about 32 hours after oral administration of a single dose of said drug to human patients in the morning.

Claim 28. (Original) The controlled release oral solid dosage form of claim 27, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at about 16 to about 32 hours after oral administration of a single dose after breakfast (in the fed state).

Claim 29. (Original) The controlled release oral solid dosage form of claim 28, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of the drug from about 1.5 ng/ml to about 4.5 ng/ml, based on a 40 mg dose of lovastatin, after oral administration of a single dose after breakfast (in the fed state).

Claim 30. (Cancelled)

Claim 31. (Original) The controlled release oral solid dosage form of claim 1, which when administered in the morning in the fed state, provides a mean time to maximum plasma concentration (T_{max}) which occurs at from about 22 to about 26 hours after administration.

Claim 32. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin, said dosage form providing a mean maximum plasma concentration (C_{max}) of lovastatin from about 1.5 ng/ml to about 7.1 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients.

Claim 33. (Original) The controlled release oral solid dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) at about 10.4 to about 20.6 hours after oral administration to human patients after administration of a single dose of said drug at dinner time.

Claim 34. (Original) The controlled release oral solid dosage form of claim 33, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1.9 ng/ml to about 4.4 ng/ml, based on a 40 mg dose of lovastatin.

Claim 35. (Original) The controlled release oral solid dosage form of claim 33, which provides a mean time to maximum plasma concentration (T_{max}) at about 13.5 to about 17.5 hours after oral administration at dinner time.

Claim 36. (Original) The controlled release oral solid dosage form of claim 35, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of lovastatin of about 3 ng/ml, based on a 40 mg dose of lovastatin.

Claim 37. (Previously presented) The controlled release oral solid dosage form of claim 1, which dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours after oral administration to a human patient after administration of a single dose of said drug to human patients at bedtime.

Claim 38. (Original) The controlled release oral solid dosage form of claim 37, which dosage form provides a mean time to maximum plasma concentration (T_{max}) at about 14.2 to about 16.9 hours after oral administration of a single dose of said drug to human patients at bedtime.

Claim 39. (Previously presented) The controlled release oral solid dosage form of claim 1, which dosage form provides a mean time to maximum plasma concentration (T_{max}) at 10 to about 22 hours at steady-state after oral administration to human patients at bedtime.

Claim 40. (Original) The controlled release oral solid dosage form of claim 39, which dosage form provides a mean time to maximum plasma concentration (T_{max}) at about 12 to about 16 hours at steady-state after oral administration to human patients at bedtime.

Claim 41. (Original) The controlled release oral solid dosage form of claim 39, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin.

Claim 42. (Original) The controlled release oral solid dosage form of claim 40, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of the drug of about 4 ng/ml, based on a 40 mg dose of lovastatin, after oral administration of a single dose at bedtime.

Claim 43. (Original) The controlled release oral solid dosage form of claim 1, wherein the drug is selected from the group consisting of lovastatin, a derivative of lovastatin, an active metabolite of lovastatin, and mixtures thereof.

Claim 44. (Original) The controlled release oral solid dosage form of claim 3, which provides a mean time to maximum plasma concentration about 14 to about 24 hours after oral administration.

Claim 45. (Original) The controlled release dosage form of claim 44, wherein the drug is lovastatin, said dosage form providing a mean maximum plasma concentration (C_{max}) of lovastatin from about 1.5 ng/ml to about 7.1 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients.

Claim 46. (Original) The controlled release dosage form of claim 44, wherein the drug is lovastatin, said dosage form providing a maximum plasma concentration (C_{max}) of the drug of from about 3 ng/ml to about 4 ng/ml (based on a 40 mg dose of lovastatin), after administration to human patients.

Claim 47. (Previously presented) The controlled release oral solid dosage form of claim 44, which achieves an accumulation of lovastatin at steady-state conditions of about 1.4- to about 2-fold the levels attained by immediate release lovastatin administered once daily.

Claim 48. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form which provides a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration of said dosage form to human patients.

Claim 49. (Original) The method of claim 48, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of lovastatin from about 1 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients.

Claim 50. (Original) The method of claim 48, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of lovastatin from about 1.5 ng/ml to about 7.1 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients

Claim 51. (Original) A method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients in the morning, which dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at about 11 to about 32 hours after oral administration to human patients.

Claim 52. (Original) The method of claim 51, wherein the drug is lovastatin.

Claim 53. (Original) The method of claim 51, wherein the T_{max} occurs at about 16.3 to about 24 hours after administration.

Claim 54. (Original) The method of claim 51, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1.5 ng/ml to about 6.9 ng/ml, based on a 40 mg dose of lovastatin.

Claims 55-56. (Cancelled)

Claim 57. (Original) The method of claim 51, further comprising administering the dosage form in the morning in the fed state, such that the time to maximum plasma concentration (T_{max}) occurs from about 22 to about 26 hours after administration.

Claim 58. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients at dinner time, which dosage form provides a mean time to maximum plasma concentration (T_{max}) at 10.4 to about 20.6 hours after oral administration of a single dose of lovastatin to a population of human patients.

Claim 59. (Original) The method of claim 58, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1.9 ng/ml to about 4.4 ng/ml, based on a 40 mg dose of lovastatin.

Claim 60. (Original) The method of claim 58, wherein the mean time to maximum plasma concentration (T_{max}) occurs at from about 13.5 hours to about 17.5 hours after oral administration.

Claim 61. (Original) The method of claim 60, wherein the drug is lovastatin, and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug of about 3 ng/ml, based on a 40 mg dose of lovastatin.

Claim 62. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients at bedtime, which dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours after oral administration.

Claim 63. (Original) The method of claim 62, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin.

Claim 64. (Original) The method of claim 62, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at about 14.2 to about 16.9 hours after oral administration of a single dose.

Claim 65. (Original) The method of claim 62, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of the drug of about 4 ng/ml, based on a 40 mg dose of lovastatin, after oral administration of a single dose.

Claim 66. (Original) The method of claim 62, wherein said T_{max} occurs at about 10 to about 22 hours after oral administration to human patients at steady-state.

Claim 67. (Original) The method of claim 62, wherein said T_{max} occurs at about 12 to about 16 hours after oral administration.

Claim 68. (Original) The method of claim 66, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 3 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin at steady-state.

Claim 69. (Original) The method of claim 66, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug of about 5.5 ng/ml.

Claim 70. (Previously presented) A method for improving the dose-response relationship achieved via the administration of a statin drug orally administered in immediate release form, comprising orally administering the statin in a controlled release dosage form which provides a mean time to maximum plasma concentration (T_{max}) of the statin drug which occurs at 10 to about 32 hours after oral administration to human patients.

Claim 71. (Previously presented) A method for providing increased systemic bioavailability of lovastatin, while at the same time not increasing the bioavailability of lovastatin acid, compared to an immediate release reference standard form of lovastatin, comprising preparing a controlled release oral solid dosage form of lovastatin which comprises a therapeutically effective amount of lovastatin and a sufficient amount of a controlled release carrier such that the controlled release dosage form provides a dissolution of from about 0% to about 25% lovastatin released after 2 hours; from about 40% to about 85% lovastatin released after 6 hours; and not less than about 75%

lovastatin released after 16 hours, when measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C and 50rpm, and such that said dosage form provides a mean time to maximum plasma concentration (T_{max}) of said lovastatin from 10 to about 32 hours after oral administration to human patients, and administering said dosage form to human patients on a once-a-day basis.

Claims 72-75. (Cancelled)

Claim 76. (Previously presented) A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime.

Claim 77. (Previously presented) A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.6 to about 23.2 (16.9 ± 6.3) hours after oral administration to human patients at bedtime.

Claim 78. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime, which dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime.

Claim 79. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime, which dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.6 to about 23.2 (16.9 ± 6.3) hours after oral administration to human patients at bedtime.

Claim 80. (Previously presented) A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal.

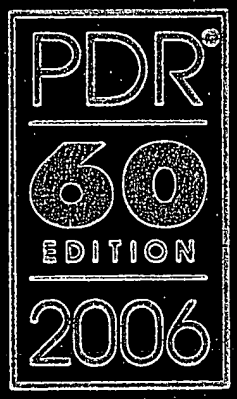
Claim 81. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime, which dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal.

IX. EVIDENCE APPENDIX

- U.S. Patent No. 5,376,383 to Alberts et al., cited by Examiner in Final Office Action of July 21, 2005
- U.S. Patent No. 5,837,379 to Chen et al., cited by Examiner in Final Office Action of July 21, 2005
- U.S. Patent No. 6,485,748 to Chen et al., cited by Examiner in Final Office Action of July 21, 2005
- Gregory A. McClelland, et al., Enhancement of 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Efficacy Through Administration of a Controlled-Porosity Osmotic Pump Dosage Form, Pharmaceutical Research, Vol. 8., No. 7. 1991, submitted by Appellants in Supplemental Response of April 7, 2006
- The Physician's Desk Reference, 2006 Edition, pages 2730-2735, submitted by Appellants in Supplemental Response of May 23, 2006

X. RELATED PROCEEDINGS APPENDIX

-None-



www.PDR.net

*mobile*PDR

PHYSICIANS' DESK REFERENCE®

PDR®
60
EDITION
2006

PHYSICIANS' DESK REFERENCE®

Senior Vice President, PDR Sales and Marketing: Dikran N. Barsamian
Vice President, Product Management: William T. Hicks
Vice President, Regulatory Affairs: Mukesh Mehta, RPh
Vice President, PDR Services: Brian Holland
Senior Directors, Pharmaceutical Solutions Sales: Chantal Corcos, Anthony Sorce
National Solutions Managers: Frank Karkowsky, Marion Reid, RPh
Senior Solutions Managers: Debra Goldman, Elaine Musco, Warner Stuart, Suzanne E. Yarrow, RN
Solutions Managers: Eileen Bruno, Cory Coleman, Marjorie A. Jaxel, Kevin McGlynn, Lois Smith, Richard Zwickel
Sales Coordinators: Arlene Phayre, Janet Wallendal

Senior Director, Brand and Product Management: Valerie E. Berger
Associate Product Managers: Michael Casale, Andrea Colavecchio
Senior Director, Publishing Sales and Marketing: Michael Bennett
Director, Trade Sales: Bill Gaffney
Associate Director, Marketing: Jennifer M. Fronzaglia
Senior Marketing Manager: Kim Marich
Direct Mail Manager: Lorraine M. Loening
Manager, Marketing Analysis: Dina A. Maeder
Promotion Manager: Linda Levine

Director of Operations: Robert Klein
Director, PDR Operations: Jeffrey D. Schaefer
Director of Finance: Mark S. Ritchin

Director, Client Services: Stephanie Struble
Director, Clinical Content: Thomas Fleming, PharmD
Director, Editorial Services: Bette LaGow

Drug Information Specialists: Michael DeLuca, PharmD, MBA; Kajal Solanki, PharmD; Greg Tallis, RPh
Project Editors: Neil Chesanow, Harris Fleming
Senior Editor: Lori Murray
Senior Production Editor: Gwynned L. Kelly

Manager, Production Purchasing: Thomas Westburgh
PDR Production Manager: Steven Maher
Production Manager: Gayle Graizzaro
Production Specialist: Christina Klinger
Senior Production Coordinators: Gianna Caradonna, Yasmin Hernández
Production Coordinator: Nick W. Clark
Senior Index Editors: Noel Deloughery, Shannon Reilly
Format Editor: Michelle G. Auffant
Traffic Assistant: Kim Condon

Production Design Supervisor: Adeline Rich
Senior Electronic Publishing Designer: Livio Udina
Electronic Publishing Designers: Bryan C. Dix, Carrie Faeth, Monika Popowitz
Production Associate: Joan K. Akerlind
Digital Imaging Manager: Christopher Husted
Digital Imaging Coordinator: Michael Labruyere

ISBN: 1-56363-526-7

InnoPran XL—Cont.

Caution should be exercised when administering InnoPran XL with drugs that slow A-V nodal conduction, e.g., digitalis, lidocaine and calcium channel blockers.

Calcium Channel Blockers

Caution should be exercised when patients receiving a beta-blocker are administered a calcium-channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction.

There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers.

Co-administration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high degree heart block, and heart failure.

Inotropic Agents

Patients on long-term therapy with propranolol may experience uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-receptor stimulation. Epinephrine is therefore not indicated in the treatment of propranolol overdose (see OVERDOSAGE).

Isoproterenol and Dobutamine

Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in patients undergoing evaluation for myocardial ischemia.

Reserpine

Patients receiving catecholamine-depleting drugs, such as reserpine and InnoPran XL, should be closely observed for excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension. Administration of reserpine with propranolol may also potentiate depression.

Non-Cardiovascular Drugs

Anesthetic Agents

Methoxyflurane and trichloroethylene may depress myocardial contractility when administered with propranolol.

Antidepressants

The hypotensive effects of MAO inhibitors or tricyclic antidepressants may be exacerbated when administered with beta-blockers by interfering with the beta-blocking activity of propranolol.

Neuroleptic Drugs

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Non-Steroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDS) have been reported to blunt the antihypertensive effect of beta-adrenoreceptor blocking agents.

Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and heart rate.

Thyroxine

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Warfarin

Propranolol when administered with warfarin increases the concentration of warfarin. Prothrombin time, therefore, should be monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In dietary administration studies in which mice and rats were treated with propranolol for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area basis, this dose in the mouse and rat is, respectively, about equal to and about twice the maximum recommended human oral daily dose (MRHD) of 640 mg propranolol. In a study in which both male and female rats were exposed to propranolol in their diets at concentrations of up to 0.05% (about 50 mg/kg body weight and less than the MRHD), from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol in bacteria (S. typhimurium strain TA 1538).

Pregnancy: Pregnancy Category C

In a series of reproductive and developmental toxicology studies, propranolol was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day, but not at doses of 80 mg/kg/day (equivalent to the MRHD on a body surface area basis), treatment was associated with embryotoxicity (reduced litter size and increased resorption rates) as well as neonatal toxicity (deaths). Propranolol also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (about 5 times the maximum recommended human oral daily dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation has been reported for neonates whose mothers received propranolol during pregnancy. Neonates whose mothers received propranolol during labor may exhibit bradycardia, hypoglycemia, and respiratory depression. Propranolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Propranolol is excreted in human milk. Caution should be exercised when InnoPran XL is administered to a nursing mother.

Pediatric Use

Safety and effectiveness of propranolol in pediatric patients have not been established.

Geriatric Use

Clinical studies of InnoPran XL did not include sufficient numbers of subjects ages 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse events occurring at a rate of ≥3%, excluding those reported more commonly in placebo encountered in the InnoPran XL placebo-controlled hypertension trials and are plausibly related to treatment, are shown in Table 1.

Table 1. Treatment Emergent Adverse Events Reported in ≥ 3% of Subjects

	InnoPran XL		
Body System	Placebo (N=88)	80 mg (N=89)	120 mg (N=85)
Fatigue	3 (3.0%)	4 (5.0%)	6 (7.0%)
Dizziness (except vertigo)	2 (2.0%)	6 (7.0%)	3 (4.0%)
Constipation	0	3 (3.0%)	1 (1.0%)

The following adverse events were observed and have been reported with use of formulations of sustained- or immediate-release propranolol.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate-release formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat; laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Autoimmune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION

InnoPran XL should be administered once daily at bedtime (approximately 10 PM) and should be taken consistently either on an empty stomach or with food. The starting dose is 80 mg but dosage should be individualized and titration may be needed to a dose of 120 mg. In the clinical trial, doses of InnoPran XL above 120 mg had no additional effects on blood pressure (See PHARMACODYNAMICS AND CLINICAL EFFECTS). The time needed for full antihypertensive response is variable, but is usually achieved within 2-3 weeks.

OVERDOSAGE

Most overdoses of propranolol are mild and respond to supportive care.

Propranolol is not significantly dialyzable. In the event of overdose or exaggerated response, the following measures should be employed:

Decontamination: Gastric lavage

Supportive Therapy

Hypotension and bradycardia have been reported following propranolol overdose and should be treated appropriately. Glucagon can exert potent inotropic and chronotropic effects and may be particularly useful for the treatment of hypotension or depressed myocardial function after a propranolol, however, may provoke uncontrolled hypertension. Bradycardia can be treated with atropine or isoproterenol. Serious bradycardia may require temporary cardiac pacing.

The electrocardiogram, pulse, blood pressure, neurobehavioral status and intake and output balance must be monitored. Isoproterenol and aminophylline may be used for bronchospasm.

HOW SUPPLIED

InnoPran XL (propranolol hydrochloride) Extended Release Capsules

Each gray/white capsule, imprinted with "80", 2 segmented bands, "RD201", and Reliant logo contains 80 mg of propranolol hydrochloride in bottles of 30 (NDC 65726-250-10), bottles of 100 (NDC 65726-250-25), bottles of 500 (NDC 65726-250-35), and a Unit Dose package of 100 (NDC 65726-250-90).

Each gray/off-white capsule, imprinted with "120", 3 segmented bands "InnoPran XL" and Reliant logo contains 120 mg of propranolol hydrochloride in bottles of 30 (NDC 65726-251-10), bottles of 100 (NDC 65726-251-25), bottles of 500 (NDC 65726-251-35) , and a Unit Dose package of 100 (NDC 65726-251-90).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a tightly closed container. The unit dose packaging should be stored in the carton.

Rx only

April 2004

Reliant

PHARMACEUTICALS LLC

Manufactured for:

Reliant Pharmaceuticals

Liberty Corner, NJ 07938

By:

Eurand America, Inc.

Vandalia, OH 45377

Address Medical Inquiries to:

Reliant Pharmaceuticals

Medical Affairs

110 Allen Road

Liberty Corner, NJ 07938 225R000

Shown in Product Identification Guide, page 331

LESCOL®

(fluvastatin sodium)

Capsules

LESCOL® XL

(fluvastatin sodium)

Extended-Release Tablets

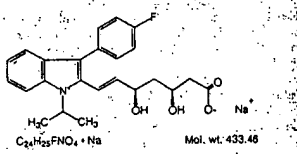
Rx only

Prescribing Information

DESCRIPTION

Lescol® (fluvastatin sodium), is a water-soluble cholesterol-lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Fluvastatin sodium is [*R**, *S**-(*E*)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4 \cdot Na$, its molecular weight is 433.46 and its structural formula is:



$C_{24}H_{25}FNO_4 \cdot Na$ Mol. wt. 433.46

This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. Lescol is supplied as capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration. Lescol® XL (fluvastatin sodium) is supplied as extended-release tablets containing fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral administration.

Active Ingredient: fluvastatin sodium

Inactive Ingredients in capsules: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients.

Capsules may also include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

Inactive Ingredients in extended-release tablets: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, potassium bicarbonate, povidone, magnesium stearate, iron oxide yellow, titanium dioxide and

lipoprotein cholesterol (LDL-C), triglycerides (TG) and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In patients with hypercholesterolemia and mixed dyslipidemia, treatment with Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium) reduced Total-C, LDL-C, apolipoprotein B, and triglycerides while producing an increase in HDL-C. Increases in HDL-C are greater in patients with low HDL-C (<35 mg/dL). Neither agent had a consistent effect on either Lp(a) or fibrinogen. The effect of Lescol or Lescol XL induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular mortality has not been determined.

Mechanism of Action

Lescol is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

Pharmacokinetics/Metabolism

Oral Absorption

Fluvastatin is absorbed rapidly and completely following oral administration of the capsule, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9%-50%). Administration with food reduces the rate but not the extent of absorption. At steady-state, administration of fluvastatin with the evening meal results in a two-fold decrease in C_{max} and more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant differences in extent of absorption or in the lipid-lowering effects were observed between the two administrations. After single or multiple doses above 20 mg, fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations.

Fluvastatin has two optical enantiomers, an active 3R, 5S and an inactive 3S,5R form. In vivo studies showed that stereo-selective hepatic binding of the active form occurs during the first pass resulting in a difference in the peak levels of the two enantiomers, with the active to inactive peak concentration ratio being about 0.7. The approximate ratio of the active to inactive approaches unity after the peak is seen and thereafter the two enantiomers decline with the same half-life. After an intravenous administration, bypassing the first-pass metabolism, the ratios of the enantiomers in plasma were similar throughout the concentration-time profiles.

Fluvastatin administered as Lescol XL 80 mg tablets reaches peak concentration in approximately 3 hours under fasting conditions, after a low-fat meal, or 2.5 hours after a low-fat meal. The mean relative bioavailability of the XL tablet is approximately 29% (range: 9%-66%) compared to that of the Lescol immediate release capsule administered under fasting conditions. Administration of a high fat meal delayed the absorption (T_{max}: 6H) and increased the bioavailability of the XL tablet by approximately 50%. Once Lescol XL begins to be absorbed, fluvastatin concentrations rise rapidly. The maximum concentration seen after a high fat meal is much less than the peak concentration following a single dose or twice daily dose of the 40 mg Lescol capsule. Overall variability in the pharmacokinetics of Lescol XL is large (42%-64% CV for C_{max} and AUC), and especially so after a high fat meal (63%-89% for C_{max} and AUC). Intra-subject variability in the pharmacokinetics of Lescol XL under fasting conditions (about 25% for C_{max} and AUC) tends to be much smaller as compared to the overall variability. Multiple peaks in plasma fluvastatin concentrations have been observed after Lescol XL administration.

Distribution

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 0.35 L/kg. The parent drug is targeted to the liver and no active metabolites are present systemically. At therapeutic concentrations, the protein binding of fluvastatin is not affected by warfarin, salicylic acid and glyburide.

Metabolism

In vitro studies demonstrated that fluvastatin undergoes oxidative metabolism, predominantly via 2C9 isozyme systems (75%). Other isozymes that contribute to fluvastatin metabolism are 2C8 (~5%) and 3A4 (~20%). *(See PRECAUTIONS: Drug Interactions Section).*

Elimination

Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug. Urinary recovery is about 5%. After a radiolabeled dose of fluvastatin, the clearance was 0.8 L/h/kg. Following multiple oral doses of radiolabeled compound, there was no accumulation of fluvastatin; however, there was a 2.3 fold accumulation of total radioactivity.

Steady-state plasma concentrations show no evidence of accumulation of fluvastatin following immediate release capsule administration of up to 80 mg daily, as evidenced by a beta-elimination half-life of less than 3 hours. However, under conditions of maximum rate of absorption (i.e., fasting) systemic exposure to fluvastatin is increased 33% to 53% compared to a single 20 mg or 40 mg dose of the immediate release capsule. Following once daily administration of the 80 mg Lescol XL tablet for 7 days, systemic exposure to fluvastatin is increased (20%-30%) compared to a single dose of the 80 mg Lescol XL tablet. Terminal half-life of Lescol XL was about 9 hours as a result of the slow-release formulation.

Single-dose and steady-state pharmacokinetic parameters in 33 subjects with hypercholesterolemia for the capsules and in 35 healthy subjects for the extended-release tablets are summarized below:

[See table 1 above]

Special Populations

Renal Insufficiency: No significant (<6%) renal excretion of fluvastatin occurs in humans.

Hepatic Insufficiency: Fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is eliminated primarily via the biliary route. Therefore, the potential exists for drug accumulation in patients with hepatic insufficiency. Caution should therefore be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see WARNINGS).*

Fluvastatin AUC and C_{max} values increased by about 2.5 fold in hepatic insufficiency patients. This result was attributed to the decreased presystemic metabolism due to hepatic dysfunction. The enantiomer ratios of the two isomers the immediate release capsule. This is most likely due to body weight differences, as adjusting for body weight decreases the magnitude of the differences seen. For Lescol XL, there are 67% and 77% increases in systemic availability for women over men under fasted and high fat meal conditions.

Pediatric: No data are available. Fluvastatin is not indicated for use in the pediatric population.

Table 1
Single-Dose and Steady-State Pharmacokinetic Parameters

	C_{max} (ng/mL) mean ± SD (range)	AUC (ng·h/mL) mean ± SD (range)	t_{max} (hr) mean ± SD (range)	CL/F (L/hr) mean ± SD (range)	$t_{1/2}$ (hr) mean ± SD (range)
Capsules					
20 mg single dose (n=17)	166±106 (48.9-517)	207±65 (111-288)	0.9±0.4 (0.5-2.0)	107±38.1 (69.5-181)	2.5±1.7 (0.5-6.6)
20 mg twice daily (n=17)	200±86 (71.8-366)	275±111 (91.6-467)	1.2±0.9 (0.5-4.0)	87.8±45 (42.8-218)	2.8±1.7 (0.9-6.0)
40 mg single dose (n=16)	273±189 (72.8-812)	456±259 (207-1221)	1.2±0.7 (0.75-3.0)	108±44.7 (32.8-193)	2.7±1.3 (0.8-5.9)
40 mg twice daily (n=16)	432±236 (119-990)	697±275 (359-1559)	1.2±0.6 (0.5-2.5)	64.2±21.1 (25.7-111)	2.7±1.3 (0.7-5.0)
Extended-Release Tablets 80 mg single dose (n=24)					
80 mg single dose, fasting (n=24)	126±53 (37-242)	579±341 (144-1760)	3.2±2.6 (1-12)		
80 mg single dose, fed-state high fat meal (n=24)	183±163 (21-733)	861±632 (199-3132)	6 (2-24)		
Extended-Release Tablets 80 mg following 7 days dosing (steady-state) (n=11)					
80 mg once daily, fasting (n=11)	102±42 (43.9-181)	630±326 (247-1406)	2.6±0.91 (1.5-4)		

Table 2
Median Percent Change in Lipid Parameters from Baseline to Week 24 Endpoint
All Placebo-Controlled Studies (Lescol®) and Active Controlled Trials (Lescol® XL)

Dose	Total Chol. N	Total Chol. % Δ	TG N	TG % Δ	LDL N	LDL % Δ	Apo B N	Apo B % Δ	HDL N	HDL % Δ
All Patients										
Lescol 20 mg[1]	747	-17	747	-12	747	-22	114	-19	747	+3
Lescol 40 mg[1]	748	-19	748	-14	748	-25	125	-18	748	+4
Lescol 40 mg twice daily[1]	257	-27	257	-18	257	-36	232	-28	257	+6
Lescol XL 80 mg[2]	750	-25	750	-19	748	-35	745	-27	750	+7
Baseline TG ≥200 mg/dL										
Lescol 20 mg[1]	148	-16	148	-17	148	-22	23	-19	148	+6
Lescol 40 mg[1]	179	-18	179	-20	179	-24	47	-18	179	+7
Lescol 40 mg twice daily[1]	76	-27	76	-23	76	-35	69	-28	76	+9
Lescol XL 80 mg[2]	239	-25	239	-25	237	-33	235	-27	239	+11

[1]Data for Lescol from 12 placebo controlled trials
[2]Data for Lescol XL 80 mg tablet from three 24 week controlled trials

CLINICAL STUDIES

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

In 12 placebo-controlled studies in patients with Type IIa or IIb hyperlipoproteinemia, Lescol® (fluvastatin sodium) alone was administered to 1621 patients in daily dose regimens of 20 mg, 40 mg, and 80 mg (40 mg twice daily) for at least 6 weeks duration. After 24 weeks of treatment, daily doses of 20 mg, 40 mg, and 80 mg (40 mg twice daily) resulted in median LDL-C reductions of 22% (n=747), 25% (n=748) and 36% (n=257), respectively. Lescol treatment produced dose-related reductions in Apo B and in triglycerides and increases in HDL-C. The median (25^{th}, 75^{th} percentile) percent changes from baseline in HDL-C after 12 weeks of treatment with Lescol at daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) were +2 (-4,+10), +5 (-2,+12), and +4 (-3,+12), respectively. In a subgroup of patients with primary mixed dyslipidemia, defined as baseline TG levels ≥200 mg/dL, treatment with Lescol also produced significant decreases in Total-C, LDL-C, TG and Apo B and variable increases in HDL-C. The median (25^{th},75^{th} percentile) percent changes from baseline in HDL-C after 12 weeks of treatment with Lescol at daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) in this population were +4 (-2,+12), +8 (+1,+15), and +4 (-3,+13), respectively.

In a long-term open-label free titration study, after 96 weeks LDL-C decreases of 25% (20 mg, n=68), 31% (40 mg, n=298) and 34% (80 mg, n=209) were seen. No consistent effect on Lp(a) was observed.

Lescol® XL (fluvastatin sodium) Extended-Release Tablets have been studied in five controlled studies of patients with Type IIa or IIb hyperlipoproteinemia. Lescol XL was administered to over 900 patients in trials from 4 to 26 weeks in duration. In the three largest of these studies, Lescol XL given as a single daily dose of 80 mg significantly reduced Total-C, LDL-C, TG and Apo B. Therapeutic response is well established within two weeks, and a maximum response is [illegible] four weeks. After four weeks of therapy, the

creases in HDL-C were also observed. The median (25th and 75th percentile) percent changes from baseline in HDL-C for Lescol XL were +7(+0,+15) after 24 weeks of treatment.

(See table 2 on previous page)

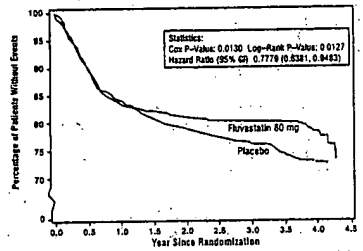
In patients with primary mixed dyslipidemia (Fredrickson Type IIb) as defined by baseline plasma triglycerides levels ≥200 mg/dL, Lescol XL 80 mg produced a median reduction in triglycerides of 25%. In these patients, Lescol XL 80 mg produced median (25th and 75th percentile) percent change from baseline in HDL-C of +11(+3,+20). Significant decreases in Total-C, LDL-C, and Apo B were also achieved. In these studies, patients with triglycerides >400 mg/dL were excluded.

Reduction in the Risk of Recurrent Cardiac Events

In the Lescol Intervention Prevention Study, the effect of Lescol 40 mg administered twice daily on the risk of recurrent cardiac events (time to first occurrence of cardiac death, nonfatal myocardial infarction, or revascularization) was assessed in 1677 patients with coronary heart disease who had undergone a percutaneous coronary intervention (PCI) procedure (mean time from PCI to randomization=3 days). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with dietary/lifestyle counseling and either Lescol 40 mg (n=844) or placebo (n=833) given twice daily for a median of 3.9 years. The study population was 84% male, 98% Caucasian, with 37% >65 years of age. At baseline patients had total cholesterol between 100 and 367 mg/dL (mean 201 mg/dL), LDL-C between 42 and 243 mg/dL (mean 132 mg/dL), triglycerides between 15 and 270 mg/dL (mean 70 mg/dL) and HDL-C between 8 and 174 mg/dL (mean 39 mg/dL).

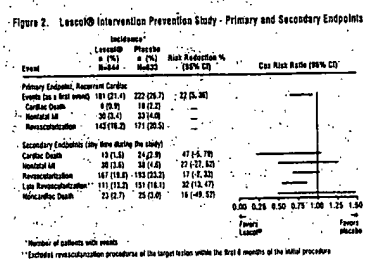
Lescol significantly reduced the risk of recurrent cardiac events (Figure 1) by 22% (p=0.013, 181 patients in the Lescol group vs. 222 patients in the placebo group). Revascularization procedures comprised the majority of the initial recurrent cardiac events (143 revascularization procedures in the Lescol group and 171 in the placebo group). Consistent trends in risk reduction were observed in patients >65 years of age.

Figure 1. Primary Endpoint - Recurrent Cardiac Events (Cardiac Death, Nonfatal MI or Revascularization Procedure) (ITT Population)



Outcome data for the Lescol Intervention Prevention Study are shown in Figure 2. After exclusion of revascularization procedures (CABG and repeat PCI) occurring within the first 6 months of the initial procedure involving the originally instrumented site, treatment with Lescol was associated with a 32% (p=0.002) reduction in risk of late revascularization procedures (CABG or PCI occurring at the original site >6 months after the initial procedure, or at another site).

Figure 2. Lescol® Intervention Prevention Study - Primary and Secondary Endpoints



*Number of patients with events

**Excludes revascularization procedures at the target lesion within the first 6 months of the initial procedure

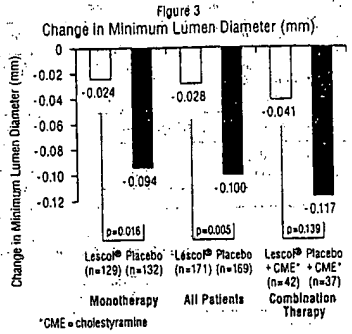
Atherosclerosis

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of Lescol therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with coronary artery disease and mild to moderate hypercholesterolemia (baseline LDL-C range 115-190 mg/dL). In this randomized double-blind, placebo controlled trial, 429 patients were treated with conventional measures (Step 1 AHA Diet) and either Lescol 40 mg/day or placebo. In order to provide treatment to patients receiving placebo with LDL-C levels >160 mg/dL at baseline, adjunctive lipid-lowering therapy was administered to patients in the study population. Quantitative coronary angiograms were evaluated at baseline and 2.5 years in 340 (79%) angiographic evaluable patients.

Lescol significantly slowed the progression of coronary atherosclerosis. Compared to placebo, Lescol significantly slowed the progression of lesions as measured by within-patient per-lesion change in minimum lumen diameter (MLD), the primary endpoint (see Figure 3 below), percent diameter stenosis (Figure 4), and the formation of new lesions (13% of all fluvastatin patients versus 22% of all placebo patients). Additionally, a significant difference in favor of Lescol was found between all fluvastatin and all placebo patients in the distribution among the three categories of definite progression, definite regression, and mixed or no change. Beneficial angiographic results (change in MLD) were independent of patients' gender and consistent across a range of baseline LDL-C levels.

Figure 3

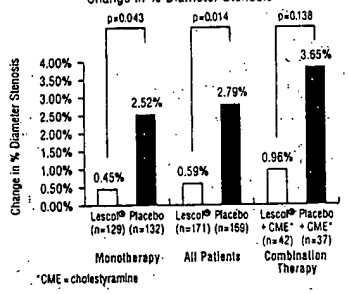
Change in Minimum Lumen Diameter (mm)



*CME = cholestyramine

Figure 4

Change in % Diameter Stenosis



*CME = cholestyramine

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program (NCEP) Treatment Guidelines, below).

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are indicated to reduce elevated total cholesterol (Total-C), LDL-C, TG and Apo B levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

Secondary Prevention of Coronary Events

In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk of undergoing coronary revascularization procedures.

Atherosclerosis

Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.

Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of fluvastatin sodium, a lipid profile should be performed to measure Total-C, HDL-C and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$$\text{LDL-C} = \text{Total-C} - \text{HDL-C} - 1/5\ \text{TG}$$

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

(See table 3 at top of next page)

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C level is ≥130 mg/dL (NCEP-ATP II).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that the LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

(See table 4 at top of next page)

Neither Lescol nor Lescol XL have been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e., hyperlipoproteinemia Types I, III, IV, or V).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases *(see WARNINGS)*.

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Fluvastatin sodium should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid lowering agents. Approximately 1.1% of patients treated with Lescol® (fluvastatin sodium) capsules in worldwide trials developed dose-related, persistent elevations of transaminase levels to more than 3 times the upper limit of normal. Fourteen of these patients (0.6%) were discontinued from therapy. In all clinical trials, a total of 33/2969 patients (1.1%) had persistent transaminase elevations with an average fluvastatin exposure of approximately 71.2 weeks; of these patients (0.6%) were discontinued. The majority of patients with these abnormal biochemical findings were asymptomatic.

In a pooled analysis of all placebo-controlled studies in which Lescol capsules were used, persistent transaminase elevations (>3 times the upper limit of normal [ULN] on two consecutive weekly measurements) occurred in 0.2%, 1.5% and 2.7% of patients treated with 20, 40, and 80 mg (or titrated to 40 mg twice daily) Lescol capsules, respectively. Ninety-one percent of the cases of persistent liver function test abnormalities (20 of 22 patients) occurred within 12 weeks of therapy and in all patients with persistent liver function test abnormalities there was an abnormal liver function test present at baseline or by week 8.

In the pooled analysis of the 24-week controlled trials, persistent transaminase elevation occurred in 1.9%, 1.8% and 4.9% of patients treated with Lescol® XL (fluvastatin sodium) 80 mg, Lescol 40 mg and Lescol 40 mg twice daily, respectively. In 13 of 16 patients treated with Lescol XL, the abnormality occurred within 12 weeks of initiation of treatment with Lescol XL 80 mg.

It is recommended that liver function tests be performed before the initiation of therapy and at 12 weeks following initiation of treatment or elevation in dose. Patients who develop transaminase elevations or signs and symptoms of liver disease should be monitored to confirm the finding and should be followed thereafter with frequent liver function tests until the levels return to normal. Should an increase in AST or ALT of three times the upper limit of normal persist (found on two consecutive occasions), withdrawal of fluvastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of Lescol and Lescol XL (see *CONTRAINDICATIONS*). Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see CLINICAL PHARMACOLOGY: Pharmacokinetics / Metabolism)*. Such patients should be closely monitored.

Skeletal Muscle

ing or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, has been reported.

Myopathy should be considered in any patients with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Fluvastatin sodium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Fluvastatin sodium therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy and or rhabdomyolysis during treatment with HMG-CoA reductase inhibitors has been reported to be increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. Myopathy was not observed in a clinical trial in 74 patients involving patients who were treated with fluvastatin sodium together with niacin.

Uncomplicated myalgia has been observed infrequently in patients treated with Lescol at rates indistinguishable from placebo.

The use of fibrates alone may occasionally be associated with myopathy. The combined use of HMG-CoA reductase inhibitors and fibrates should generally be avoided.

PRECAUTIONS

General

Before instituting therapy with Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems *(see INDICATIONS AND USAGE)*.

The HMG-CoA reductase inhibitors may cause elevation of creatine phosphokinase and transaminase levels *(see WARNINGS and ADVERSE REACTIONS)*. This should be considered in the differential diagnosis of chest pain in a patient on therapy with fluvastatin sodium.

Homozygous Familial Hypercholesterolemia

HMG-CoA reductase inhibitors are reported to be less effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Women should be informed that if they become pregnant while receiving Lescol or Lescol XL the drug should be discontinued immediately to avoid possible harmful effects on a developing fetus from a relative deficit of cholesterol and biological products derived from cholesterol. In addition, Lescol or Lescol XL should not be taken during nursing. *(See CONTRAINDICATIONS.)*

Drug Interactions

The below listed drug interaction information is derived from studies using immediate release fluvastatin. Similar studies have not been conducted using the Lescol XL tablet.

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin (See WARNINGS: Skeletal Muscle).

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (~75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e. ~5% and ~20%, respectively. If one pathway is inhibited in the elimination process of fluvastatin other pathways may compensate.

In vivo drug interaction studies with CYP3A4 inhibitors/substrates such as cyclosporine, erythromycin, and itraconazole result in minimal changes in the pharmacokinetics of fluvastatin, confirming less involvement of CYP3A4 isozyme. Concomitant administration of fluvastatin and phenytoin increased the levels of phenytoin and fluvastatin, suggesting predominant involvement of CYP2C9 in fluvastatin metabolism.

Niacin/Propranolol: Concomitant administration of immediate release fluvastatin sodium with niacin or propranolol has no effect on the bioavailability of fluvastatin sodium.

Cholestyramine: Administration of immediate release fluvastatin sodium concomitantly with, or up to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for AUC and 50%-80% for C_{max}. However, administration of immediate release fluvastatin sodium 4 hours after cholestyramine resulted in a clinically significant additive effect compared with that achieved with either component drug.

Cyclosporine: Plasma cyclosporine levels remain unchanged when fluvastatin (20 mg daily) was administered concurrently in renal transplant recipients on stable cyclosporine regimens. Fluvastatin AUC increased 1.9 fold, and C_{max} increased 1.3 fold compared to historical controls.

Table 3
NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0–1 Risk factor†††	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

†CHD, coronary heart disease

††Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g. nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

†††Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Table 4

Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations: Major	Lipid Elevations: Minor
I (rare)	Chylomicrons	TG	↑ → C
IIa	LDL	C	–
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	–
IV	VLDL	TG	↑ → C
V (rare)	Chylomicrons, VLDL	TG	↑ → C

C = cholesterol, TG = triglycerides, LDL = low density lipoprotein, VLDL = very low density lipoprotein, IDL = intermediate density lipoprotein

Erythromycin: Erythromycin (500 mg, single dose) did not affect steady-state plasma levels of fluvastatin (40 mg daily).

Itraconazole: Concomitant administration of fluvastatin (40 mg) and itraconazole (100 mg daily × 4 days) does not affect plasma itraconazole or fluvastatin levels.

Gemfibrozil: There is no change in either fluvastatin (20 mg twice daily) or gemfibrozil (600 mg twice daily) plasma levels when these drugs are co-administered.

Phenytoin: Single morning dose administration of phenytoin (300 mg extended release) increased mean steady-state fluvastatin (40 mg) C_{max} by 27% and AUC by 40% whereas fluvastatin increased the mean phenytoin C_{max} by 5% and AUC by 20%. Patients on phenytoin should continue to be monitored appropriately when fluvastatin therapy is initiated or when the fluvastatin dosage is changed.

Diclofenac: Concurrent administration of fluvastatin (40 mg) increased the mean C_{max} and AUC of diclofenac by 60% and 25% respectively.

Tolbutamide: In healthy volunteers, concurrent administration of either single or multiple daily doses of fluvastatin sodium (40 mg) with tolbutamide (1 g) did not affect the plasma levels of either drug to a clinically significant extent.

Glibenclamide (Glyburide): In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max}, AUC, and $t_{1/2}$ of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5-20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 40 mg twice daily.

Losartan: Concomitant administration of fluvastatin with losartan has no effect on the bioavailability of either losartan or its active metabolite.

Cimetidine/Ranitidine/Omeprazole: Concomitant administration of immediate release fluvastatin sodium with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24%-33%), with an 18%-23% decrease in plasma clearance.

Rifampicin: Administration of immediate release fluvastatin sodium to subjects pretreated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%), with a large increase (95%) in plasma clearance.

Warfarin: In vitro protein binding studies demonstrated no interaction at therapeutic concentrations. Concomitant administration of a single dose of warfarin (30 mg) in young healthy males receiving immediate release fluvastatin sodium (40 mg/day × 8 days) resulted in no elevation of ra-

itantly with other HMG-CoA reductase inhibitors. Therefore, patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when fluvastatin sodium is initiated or the dosage of fluvastatin sodium is changed.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Fluvastatin exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred, suggesting that the observation was not due to a direct effect upon testosterone production. No effect upon FSH in males was noted. Due to the limited number of premenopausal females studied to date, no conclusions regarding the effect of fluvastatin upon female sex hormones may be made.

Two clinical studies in patients receiving fluvastatin at doses up to 80 mg daily for periods of 24 to 28 weeks demonstrated no effect of treatment upon the adrenal response to ACTH stimulation. A clinical study evaluated the effect of fluvastatin at doses up to 80 mg daily for 28 weeks upon the gonadal response to HCG stimulation. Although the mean total testosterone response was significantly reduced ($p<0.05$) relative to baseline in the 80 mg group, it was not significant in comparison to the changes noted in groups receiving either 40 mg of fluvastatin or placebo.

Patients treated with fluvastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g., ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones.

CNS Toxicity

CNS effects, as evidenced by decreased activity, ataxia, loss of righting reflex, and ptosis were seen in the following animal studies: the 18-month mouse carcinogenicity study at 50 mg/kg/day, the 6-month dog study at 36 mg/kg/day, the 6-month hamster study at 40 mg/kg/day, and in acute, high-dose studies in rats and hamsters (50 mg/kg), rabbits (300 mg/kg) and mice (1500 mg/kg). CNS toxicity in the acute high-dose studies was characterized (in mice) by conspicuous vacuolation in the ventral white columns of the spinal cord at a dose of 5000 mg/kg and (in rat) by edema with separation of myelinated fibers of the ventral spinal tracts and sciatic nerve at a dose of 1500 mg/kg. CNS toxicity, characterized by periaxonal vacuolation, was observed in the medulla of dogs that died after treatment for 5 weeks

hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. No CNS lesions have been observed after chronic treatment for up to 2 years with fluvastatin in the mouse (at doses up to 350 mg/kg/day), rat (up to 24 mg/kg/day), or dog (up to 16 mg/kg/day).

Prominent bilateral posterior Y suture lines in the ocular lens were seen in dogs after treatment with 1, 8, and 16 mg/kg/day for 2 years.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year study was performed in rats at dose levels of 6, 9, and 18-24 (escalated after 1 year) mg/kg/day. These treatment levels represented plasma drug levels of approximately 9, 13, and 26-35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and 1 carcinoma of the forestomach at the 24 mg/kg/day dose level was considered to reflect the prolonged hyperplasia induced by direct contact exposure to fluvastatin sodium rather than to a systemic effect of the drug. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded for males treated with 18-24 mg/kg/day. The increased incidence of thyroid follicular cell neoplasm in male rats with fluvastatin sodium appears to be consistent with findings from other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg/day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg/day and in females at 15 mg/kg/day. These treatment levels represented plasma drug levels of approximately 0.05, 2, and 7 times the mean human plasma drug concentration after a 40 mg oral dose.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese Hamster cells; HGPRT V79 Chinese Hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.

In a study in rats at dose levels for females of 0.6, 2 and 6 mg/kg/day and at dose levels for males of 2, 10 and 20 mg/kg/day, fluvastatin sodium had no adverse effects on the fertility or reproductive performance.

Seminal vesicles and testes were small in hamsters treated for 3 months at 20 mg/kg/day (approximately three times the 40 milligram human daily dose based on surface area, mg/m^2). There was tubular degeneration and aspermatogenesis in testes as well as vesiculitis of seminal vesicles. Vesiculitis of seminal vesicles and edema of the testes were also seen in rats treated for 2 years at 18 mg/kg/day (approximately 4 times the human C_{max} achieved with a 40 milligram daily dose).

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Fluvastatin sodium produced delays in skeletal development in rats at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced maternal toxicity. These doses resulted in 2 times (rat at 12 mg/kg) or 5 times (rabbit at 10 mg/kg) the 40 mg human exposure based on mg/m^2 surface area. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at 2 mg/kg/day. A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study with neonatal mortality beginning at 6 mg/kg. A modified Segment III study was performed at dose levels of 12 or 24 mg/kg/day with or without the presence of concurrent supplementation with mevalonic acid, a product of HMG-CoA reductase which is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the maternal and neonatal mortality but did not prevent low body weights in pups at 24 mg/kg on days 0 and 7 postpartum. Therefore, the maternal and neonatal lethality observed with fluvastatin sodium reflect its exaggerated pharmacologic effect during pregnancy. There are no data with fluvastatin sodium in pregnant women. However, rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. Lescol or Lescol XL should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If a woman becomes pregnant while taking Lescol or Lescol XL, the drug should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Based on preclinical data, drug is present in breast milk in a 2:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, nursing women should not take Lescol or Lescol XL *(see CONTRAINDICATIONS).*

Pediatric Use

Safety and effectiveness in individuals less than 18 years old have not been established. Treatment in patients less than 18 years of age is not recommended at this time.

Geriatric Use

The effect of age on the pharmacokinetics of immediate release fluvastatin sodium was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary as a function of age. *(See also CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism.)* Elderly patients (≥65 years of age) demonstrated a greater treatment response in respect to LDL-C, Total-C and LDL/HDL ratio than patients <65 years of age.

ADVERSE REACTIONS

In all clinical studies of Lescol® (fluvastatin sodium), 1.0% (32/2969) of fluvastatin-treated patients were discontinued due to adverse experiences attributed to study drug (mean exposure approximately 16 months ranging in duration from 1 to >36 months). This results in an exposure adjusted rate of 0.8% (32/4051) per patient year in fluvastatin patients in controlled studies compared to an incidence of 1.1% (4/355) in placebo patients. Adverse reactions have usually been of mild to moderate severity.

In controlled clinical studies, 3.9% (36/912) of patients treated with Lescol® XL (fluvastatin sodium) 80 mg discontinued due to adverse events (causality not determined).

Clinically relevant adverse experiences occurring in the Lescol and Lescol XL controlled studies with a frequency >2%, regardless of causality, include the following:

Table 5

Clinically Relevant Adverse Experiences Occurring in >2% Patients in Lescol® and Lescol XL® Controlled Studies

Adverse Event	Lescol®[1] (%) (N=2326)	Placebo[1] (%) (N=960)	Lescol® XL[2] (%) (N=912)
Musculoskeletal			
Myalgia	5.0	4.5	3.8
Arthritis	2.1	2.0	1.3
Arthropathy	NA	NA	3.2
Respiratory			
Sinusitis	2.6	1.9	3.5
Bronchitis	1.8	1.0	2.6
Gastrointestinal			
Dyspepsia	7.9	3.2	3.5
Diarrhea	4.9	4.2	3.3
Abdominal Pain	4.9	3.8	3.7
Nausea	3.2	2.0	2.5
Flatulence	2.6	2.5	1.4
Psychiatric Disorders			
Insomnia	2.7	1.4	0.8
Genitourinary			
Urinary Tract Infection	1.6	1.1	2.7
Miscellaneous			
Headache	8.9	7.8	4.7
Influenza-Like Symptoms	5.1	5.7	7.1
Accidental Trauma	5.1	4.8	4.2
Fatigue	2.7	2.3	1.6
Allergy	2.3	2.2	1.0

[1] Controlled trials with Lescol Capsules (20 and 40 mg daily and 40 mg twice daily)

[2] Controlled trials with Lescol XL 80 mg Tablets

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with fluvastatin sodium therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Concomitant Therapy

Fluvastatin sodium has been administered concurrently with cholestyramine and nicotinic acid. No adverse reactions unique to the combination or in addition to those previously reported for this class of drugs alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. *(See WARNINGS: Skeletal Muscle.)*

OVERDOSAGE

The approximate oral LD_{50} is greater than 2 g/kg in mice and greater than 0.7 g/kg in rats.

The maximum single oral dose of Lescol® (fluvastatin sodium) capsules received by healthy volunteers was 80 mg. No clinically significant adverse experiences were seen at this dose. The maximum dose administered with an extended-release formulation was 640 mg for two weeks. This dose was not well tolerated and produced a variety of GI complaints and an increase in transaminase values (i.e., SGOT and SGPT).

There has been a single report of 2 children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 × 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialysability of fluvastatin sodium and of its metabolites in humans is not known at present.

Information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium) and should continue on this diet during treatment with Lescol or Lescol XL. (See NCEP Treatment Guidelines for details on dietary therapy.)

For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as one capsule, 80 mg as one Lescol XL tablet administered as a single dose in the evening or 80 mg in divided doses of the 40 mg capsule given twice daily. For patients requiring LDL-C reduction to a goal of <25% a starting dose of 20 mg may be used. The recommended dosing range is 20-80 mg/day. Lescol or Lescol XL may be taken without regard to meals, since there are no apparent differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C of a given dose are seen within 4 weeks, periodic lipid determinations should be performed and dosage adjustment made according to the patient's response to therapy and established treatment guidelines. The therapeutic effect of Lescol or Lescol XL is maintained with prolonged administration.

Concomitant Therapy

Lipid-lowering effects on total cholesterol and LDL cholesterol are additive when immediate release Lescol is combined with a bile-acid binding resin or niacin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium, Lescol should be administered at bedtime, at least 2 hours following the resin to avoid a significant interaction due to drug binding to resin. *(See also ADVERSE REACTIONS: Concomitant Therapy.)*

Dosage in Patients with Renal Insufficiency

Since fluvastatin sodium is cleared hepatically with less than 6% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not necessary. Fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment; therefore caution should be exercised when treating such patients at higher doses.

HOW SUPPLIED

Lescol® (fluvastatin sodium) Capsules

20 mg

Brown and light brown imprinted twice with "Δ" and "20" on one half and and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.

Bottles of 30 capsules ..... (NDC 0078-0176-15)

Bottles of 100 capsules ..... (NDC 0078-0176-05)

40 mg

Brown and gold imprinted twice with "Δ" and "40" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.

Bottles of 30 capsules ..... (NDC 0078-0234-15)

Bottles of 100 capsules ..... (NDC 0078-0234-05)

Lescol® XL (fluvastatin sodium) Extended-Release Tablets
80 mg
Yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with "Lescol XL" on one side and "80" on the other.
Bottles of 30 tablets ..... (NDC 0078-0354-15)
Bottle of 100 tablets ..... (NDC 0078-0354-05)

Store and Dispense
Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). (See USP Controlled Room Temperature). Dispense in a tight container. Protect from light.

*Trademark of Medical Economics Company, Inc.

T2003-40
REV: MAY 2003 89011108
Shown in Product Identification Guide, page 331

OMACOR®

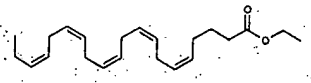
[ō-mā-kōr]

(omega-3-acid ethyl esters) Capsules

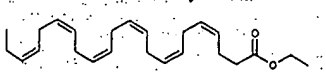
℞

DESCRIPTION

Omacor, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Omacor (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).
The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.
The structural formula of DHA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.
Omacor capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism of action of Omacor is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β-oxidation in the liver. Omacor may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies
In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Omacor) induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Omacor was independent of age (<49 years vs. ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Omacor in children are not available.

Drug Interactions
Cytochrome P450-Dependent Monooxygenase Activities
The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

The effects of Omacor 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Omacor, 42 on placebo) with very high triglyceride levels (Table 1). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.
(See table 1 above)

Table 1. Median Baseline and Percent Change From Baseline in Lipid Parameters In Patients with Very High TG Levels (≥ 500 mg/dL)

	TG		LDL-C		CHOL		HDL-C		VLDL-C		non-HDL-C	
	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg
Placebo	788	+6.7	108	-4.8	314	-1.7	24	0.0	175	-0.9	292	-3.6
Omacor 4g/day	816	-44.9	89	+44.5	296	-9.7	22	+9.1	175	-41.7	271	-13.8
Difference		-51.6		+49.3		-8.0		+9.1		-40.8		-10.2

BL = Baseline (mg/dL); % Chg = Percent Change from Baseline; Difference = Omacor - Placebo

Table 2. Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Hypertriglyceridemia That Used Omacor 4 g per Day

BODY SYSTEM Adverse Event	Omacor (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.
*Placebo was corn oil for all studies.

Omacor 4 g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Omacor treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals.
Patients should be monitored to ensure that the LDL-C level does not increase excessively.
The effect of Omacor on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of Omacor on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

INDICATIONS AND USAGE

Omacor is indicated as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.

Usage Considerations
According to accepted clinical guidelines, excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia (HTG) and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy for HTG.
The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet. (See PRECAUTIONS).

CONTRAINDICATIONS

Omacor is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General
Initial Therapy
Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Omacor therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.
Continued Therapy
Laboratory studies should be performed periodically to measure the patient's TG levels during Omacor therapy. Omacor therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.
Information for Patients
Omacor should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.
Laboratory Tests
In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Omacor therapy. In some patients, Omacor increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Omacor therapy.
Drug Interactions
Anticoagulants
Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Omacor and concomitant anticoagulants. Patients receiving treatment with both Omacor and anticoagulants should be monitored periodically.
Cytochrome P450-Dependent Monooxygenase Activities
Omega-3-fatty acid containing products have been shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Omacor to induce P450 activities in humans has not been studied.
Carcinogenesis, Mutagenesis, Impairment of Fertility
In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.
Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.
In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. It is unknown whether Omacor can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omacor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.
In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

Continued on next page